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Message Urgency: HIGH

This is a message from the Louisiana Department of Health Emergency Operations Center (LDH EOC) for the Louisiana Health Alert Network (LA HAN) recipients. This message is from Dr. Frank Welch regarding: **Multisystem Inflammatory Syndrome in children (MIS-C) associated with COVID-19.** Please share and distribute with relevant stakeholders and partners through your own distribution channels.

Background

- On May 14, 2020, the Centers for Disease Control issued a Health Alert Network Advisory regarding a multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus 2019 (COVID-19), along with a case definition for this syndrome.
- CDC reports that 570 confirmed cases of MIS-C and 10 deaths in 40 states occurred March-July 2020.
- Healthcare providers who have cared or are caring for patients younger than 21 years of age meeting MIS-C criteria should immediately report them to the Louisiana Office of Public Health Infectious Disease Epidemiology Section using the secure online portal: Infectious Disease Epidemiology COVID-19 priority event reporting portal.

MIS-C in Louisiana

- As of August 5, 2020, the Louisiana Department of Health has identified 44 cases, including 4 deaths that meet CDC criteria (see case definition below) for MIS-C.
- The 44 cases have occurred among children <1 years of age to 19 years of age with a median age of 8 years of age. More than 50% of reported cases have occurred in children who are Black or Hispanic/Latino.
- Twenty-five percent of children had involvement of 2 organ systems and 75% had involvement of three or more organ systems. Nearly all children (90%) had gastrointestinal manifestations (e.g. vomiting, diarrhea, elevated LFTs and bilirubin), two-thirds of children had some hematologic involvement (including thrombocytopenia, thrombophilia, elevated d-dimers), 50% had respiratory involvement, nearly half had dermatological (47%) or cardiac (43%) involvement. Renal and Neurologic involvement was documented in 10% of children. The majority of children had no documented underlying conditions. Seventy-three percent of cases tested positive for SARS-CoV-2.
- At this time, we do not know why MIS-C develops in some children and not in others.

Clinical presentations

Children and adolescents with MIS-C present with symptoms of persistent fever (≥24 hours) and signs and symptoms including multiorgan (e.g. cardiac, gastrointestinal, hematologic, renal, dermatologic, neurologic) involvement, and elevated inflammatory markers.
Symptoms may include but are not limited to the following:

- Abnormal vital signs (tachycardia, tachypnea, hypotension)
- Conjunctivitis, red eyes, red or swollen hands and feet, swollen glands

- Gastrointestinal symptoms: abdominal pain, diarrhea
- Dermatological manifestations: rash, red cracked lips, mucocutaneous lesions
- Respiratory distress of any severity
- Neurologic deficits or mental status changes (including subtle manifestations), headaches, meningitis
- Hematological manifestations: abnormal clotting, bleeding
- Evidence of mild renal or hepatic injury

Not all children will have the same signs and symptoms and some children may have symptoms not listed here. A child under investigation for MIS-C should also undergo evaluation for other infectious (e.g. septic shock, strep, adenovirus, norovirus) and non-infectious (e.g. malignancy, diabetes, rheumatological diseases) etiologies that may explain the clinical presentation.

Evaluation

Laboratory Testing for MIS-C may include the following:

- Identifying laboratory evidence of inflammation:
    - C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.
- SARS-CoV-2 detection by RT-PCR or antigen test is indicated.
- Where feasible, SARS-CoV-2 serology testing is suggested, even in the presence of positive RT-PCR or antigen testing. Any serology testing should be performed prior to administering IVIG or any other exogenous antibody treatments.

- Other testing to evaluate multisystem involvement should be directed by patient signs or symptoms and the multidisciplinary team managing the patient. An expanded laboratory and cardiac workup may include:
    - Chest radiograph, abdominal ultrasound or CT echocardiogram, electrocardiogram;

- Expanded laboratory tests including: cardiac enzyme or troponin testing (per the center's testing standards), B-type natriuretic peptide (BNP) or NT-proBNP;
- Triglycerides, creatine kinase, amylase, blood and urine culture, prothrombin time/partial thromboplastin time (PT/PTT), INR.

Treatment

There are currently no published guidelines or CDC recommendations regarding treatment for MIS-C and no studies comparing efficacy of various treatment options. However, the American Academy of Pediatrics and the American College of Rheumatology have recently issued guidance and there are published reports of the treatments that many institutions have been using (Behadjer, et al.; Riphagen

et al; Verdoni et al). Clinicians should use a multidisciplinary approach to guide individual patient treatment. Thus far, treatment has consisted primarily of supportive care and directed care against the underlying inflammatory process.

- fluid resuscitation;
- inotropic support;
- respiratory support; and
- in rare cases, extracorporeal membranous oxygenation (ECMO).

Anti-inflammatory measures have included the frequent use of intravenous immunoglobulin (IVIG) and steroids. The use of other anti-inflammatory medications and the use of anti-coagulation treatments have been variable. Aspirin has commonly been used due to the concern for coronary involvement, and antibiotics are routinely used to treat potential sepsis while awaiting bacterial cultures. Appropriate care may require transfer of the patient to a referral center capable of advanced pediatric intensive care.

Actions Requested of Providers

- Consider testing any patient for whom MIS-C is a clinical consideration for acute COVID-19 infection (with RT-PCR) and prior COVID-19 infection or exposure (antibody testing).
- Patients under investigation for MIS-C should also be evaluated for other infectious and non-infectious etiologies that could explain their clinical presentation. This evaluation should not be delayed pending COVID-19 PCR or serology testing.
- Please advise parents and guardians to monitor children and adolescents diagnosed with or exposed to COVID-19 patients for early signs of MIS-C (such as persistent fever, difficulty breathing, chest or abdominal pain/discomfort, mental status changes, rash, gastrointestinal symptoms) and to immediately call and/or present to a health care provider for further evaluation if symptoms develop.

Report cases that meet the CDC definition of Multisystem Inflammatory Syndrome in Children (MIS-C) to LDH within 1 working day.
How to report Suspect Cases of MIS-C: Infectious Disease Epidemiology COVID-19 priority event reporting portal

CDC Case Definition for Multisystem Inflammatory Syndrome in Children(MIS-C)

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

- **Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection**

*Fever is defined as a temperature >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours.

**Laboratory evidence of inflammation includes but is not limited to elevations in any of the following markers: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

Additional Resources

Clinical Guidance & CDC Resources

Clinical Guidance from the American Academy of Pediatrics. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance.
https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/

Clinical Guidance from the American College of Rheumatology . Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. June 17, 2020. https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf

CDC Clinical Guidance . Clinical Management of Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease (COVID-19). Webinar. Thursday, July 16, 2020.
Slides: https://emergency.cdc.gov/coca/ppt/2020/Slides_07_16_20.pdf
Recording: https://emergency.cdc.gov/coca/calls/2020/callinfo_071620.asp

CDC Health Advisory : CDCHAN-00432 May 14, 2020:
https://emergency.cdc.gov/han/2020/han00432.asp
CDC Webpage for Health Care Providers: Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children . Last updated May 29, 2020. https://www.cdc.gov/mis-c/hcp/

CDC Webpage for Parents : https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/mis-c.html

CDC Infographic : Early Cases of MIS-C: Multi-System Inflammatory Syndrome in U.S. Children. Last Updated July 16, 2020. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/infographic-mis-c.html

Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States . Last Updated July 15, 2020. https://www.cdc.gov/mis-c/cases/index.html

Reports & References

Godfred-Cato S, Bryant, B, et al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children – United States, March-July 2020. Morbidity and Mortality Weekly Report; Vol.69. Published online August 7, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

Feldstein L, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med 2020; 383:334.-346. Published online June 29, 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa2021680

Dufort EM, Koumans EH, Chow EJ, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med. 2020; 383: 347-358. Published online June 29, 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa2021756?query=recirc_curatedRelated_article

Royal College of Paediatrics and Child Health Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19, https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic . Circulation 2020. Originally published May 17, 2020. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.048360

Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020.
Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort studyexternal icon. Lancet 2020.

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